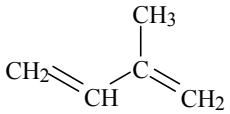
ISOPRENE
CAS No. 78-79-5
First Listed in the *Ninth Report on Carcinogens*



CARCINOGENICITY

Isoprene is *reasonably anticipated to be a human carcinogen* based on evidence of tumor formation at multiple organ sites in multiple species of experimental animals (Melnick et al., 1994; NTP 31, 1995; NTP 486, 1997 draft; Placke et al., 1996). Inhalation exposure of mice to isoprene vapors induced increased incidences of neoplasms of the lung, liver, Harderian gland, forestomach, hematopoietic system, and circulatory system. Inhalation exposure of rats to isoprene vapors induced increased incidences of neoplasms of the mammary gland, kidney, and testis.

There are no data available to evaluate the carcinogenicity of isoprene in humans.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Isoprene is the 2-methyl analog of 1,3-butadiene, an industrial chemical that has been identified as an animal and human carcinogen. Isoprene and butadiene are metabolized to monoepoxide and diepoxide intermediates by liver microsomal cytochrome P450-dependent monooxygenases from several species, including humans. Detoxification of these intermediates may occur by hydrolysis catalyzed by epoxide hydrolase or conjugation with glutathione catalyzed by glutathione-*S*-transferase. The diepoxide intermediates of isoprene and butadiene are mutagenic in *Salmonella typhimurium* whereas the parent compounds are inactive (Gervasi et al., 1985). In mice, isoprene and 1,3-butadiene induced sister chromatid exchanges in bone marrow cells and increased the frequency of micronucleated erythrocytes in peripheral blood (Tice et al., 1987; cited by NTP 486, 1997 draft; Tice et al., 1988). Common sites of neoplasm induction by isoprene and butadiene include the mammary gland and testis in rats, and the liver, lung, Harderian gland, forestomach, and circulatory system in mice (NTP 486, 1997 draft). Lung and Harderian gland neoplasms induced by isoprene in mice had a high frequency of unique K-*ras* mutations (A to T transversions at codon 61) (Hong et al., 1997).

No data are available that would suggest that mechanisms thought to account for tumor induction by isoprene in experimental animals would not also operate in humans.

PROPERTIES

Isoprene (C_5H_8, mol. wt. = 68.1) is a colorless liquid with a density of 0.6805 at 20 °C, a vapor pressure at 25 °C of 550 mm Hg, a melting point of -145.95 °C, and a boiling point of 34.067 °C. It is insoluble in cold water and soluble in ethanol and diethyl ether (Budavari, 1996; HSDB, 1997). The log of the octanol-water partition coefficient is 2.42. A concentration of 2.79 mg/m^3 in air is equivalent to 1 ppm. Isoprene is highly flammable with a flash point of -48 ºC.

It is easily ignited by heat, sparks, or flames. Vapors may form highly explosive mixtures with air and may polymerize explosively when heated. It is highly reactive, with reactions similar to those of 1,3-butadiene. In the absence of inhibitors, isoprene forms peroxides upon air exposure (HSDB, 1997; Saltman, 1985).

Isoprene is one of the major photochemically reactive hydrocarbons emitted by numerous plant species (Bowling et al., 1998). The large quantities of non-methane hydrocarbons (NMHCs) emitted by vegetation, especially in tropical and subtropical regions, influence atmospheric processes. Isoprene and other highly reactive natural alkenes can serve as precursors to formation of photochemical oxidants that contribute to regional-scale air pollution (Hoffman et al., 1996). Isoprene, the monoterpenes, and other unsaturated hydrocarbons react with hydroxyl radicals (HO•) and tropospheric ozone (O_3) and may act as photochemical smog precursors. The lifetime of atmospheric isoprene has been variously estimated to be 1.3 to 34.0 hours and 1 to 2 hours based on its rates of reactions with ozone and hydroxyl radicals (Altschuller, 1983; Guenther et al., 1995). In sunlight, ultraviolet irradiation of isoprene, other biogenic NMHCs, and anthropogenic hydrocarbons in the presence of atmospheric nitrogen oxides (NO_x) gives numerous reaction products, including acetaldehyde, acetone, carbon dioxide, carbon monoxide, formaldehyde, formic acid, and peroxyacetyl nitrates (PAN). These products plus methacrolein and methyl vinyl ketone, which are apparently specific to isoprene, represent 30 to 73% of the carbon content of the reacted isoprene (Altschuller, 1983).

USE

About 95% of isoprene production is used to produce *cis*-1,4-polyisoprene; 2%, to produce butyl rubber (isobutene-isoprene copolymer); and 3%, to produce thermoplastic, elastomeric co-block (SIS) polymers (Saltman, 1985; Taalman, 1996).

PRODUCTION

Isoprene is recovered from C_5 streams as a by-product of thermal cracking of naphtha or gas oil. The isoprene yield is about 2 to 5% of the ethylene yield (Saltman, 1985). U.S. demand for isoprene grew 6.5% annually from 1985 to 1992 (Chem. Mark. Rep., 1994; Chem. Week, 1994). In 1994, isoprene production in the United States was approximately 619 million pounds (281,000 Mg [metric tons]) (USITC, 1995), an increase of almost 29% over production in 1992 (USITC, 1994). Estimated isoprene production capacity for 8 facilities was 598 million pounds in 1996, based on estimates of isoprene content of product stream available from ethylene production via heavy liquids (SRIa, 1997).

EXPOSURE

Isoprene is formed endogenously in humans and is generally the major hydrocarbon (up to 70% in human breath (Gelmont et al., 1981). Concentrations in blood range from 15 to 70 nmol/L (1.0 to 4.8 µg/L) (Cailleux et al., 1992; cited by NTP 486, 1997 draft). Humans produce isoprene endogenously at a rate of 0.15 µmol/kg/h (Taalman, 1996) [about 17 mg/day for a 150-lb (70-kg) person]. [Endogenous production rates reported for rats and mice are 1.9 and 0.4 µmol/kg/h, respectively (Peter et al., 1987; cited by Taalman, 1996).] Ambient air concentrations of isoprene are generally less than about 10 ppb C or about 0.03 mg isoprene/m^3. Based on estimated human intake of 15 to 20 m^3 air per day, ambient air would contribute less than 0.45 to 0.6 mg/day to daily isoprene exposure. The estimate of 17 mg/day given above for

human endogenous production of isoprene is about 30- to 40-fold higher than the contribution from ambient air (calculations by ILS Inc.).

NIOSH collected data on potential exposure to isoprene in the National Occupational Hazard Survey (NOHS) from 1972 to 1974 (NIOSH, 1976) and in the National Occupational Exposure Survey (NOES) from 1981 to 1983 (NIOSH, 1990). The first survey (NIOSH, 1976) indicated that 58,000 employees in over 30 different industries were potentially exposed to isoprene. The more limited later survey of six industries showed that approximately 3,700 workers were potentially exposed to isoprene between 1981 and 1983 (NIOSH, 1990).

Isoprene is emitted from plants and trees and is widely present in the environment at low concentrations (Taalman, 1996). Isoprene global emissions—estimated at 175 to 503 million metric tons (Tg) C per year—represent about 44 to 51% of total global natural VOC emissions (Guenther et al., 1995). The average biogenic emission rate factor for isoprene in the United States is about 3 mg C/m^2/h. Isoprene concentrations in biogenic emissions range from 8% to 91% of total VOCs, with a 58% average. Since isoprene biosynthesis is associated with photosynthesis, isoprene emissions are negligible at night (Guenther et al., 1994). The south central and southeastern areas of the United States have the highest biogenic emissions. Summertime isoprene emissions are highest in each region and account for more than 50% of annual biogenic emissions (Lamb et al., 1993).

Sources of anthropogenic releases of isoprene to the atmosphere include ethylene production by cracking naphtha, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoking (3,100 µg/cigarette), gasoline, and exhaust of turbines and automobiles (HSDB, 1997).

Reported U.S. ambient air concentrations of isoprene range from 0.003 to 0.06 mg/m^3 (1 to 21 ppb), with isoprene representing less than 10% of NMHCs (Arnts and Meeks, 1980; Altschuller, 1983; Seila et al., 1984; Lawrimore and Aneja, 1997; Hagerman et al., 1997). During stagnation conditions, biogenic hydrocarbons may contribute more to total atmospheric hydrocarbons (Altschuller, 1983).

Foods of plant origin would be expected to be a source of daily exposure to isoprene since it is emitted by agricultural crops and is the basic structural unit in countless natural products found in foods such as terpenes and vitamins A and K (IARC V.60, 1994). Its occurrence has been reported in the essential oil of oranges, in the fruit of hops, and in the root of carrots (Duke, 1992).

The major source of isoprene in indoor air is environmental tobacco smoke. Isoprene was found to be the major component of hydrocarbons in the air of a smoky café (10 smoking patrons, 10 not smoking) (16.7%) and sidestream smoke (29.2%) (Barrefors and Petersson, 1993). A monitoring survey in November 1992 in homes and workplaces in the greater Philadelphia area found mean isoprene concentrations in personal air samples of 4.65 µg/m^3 in nonsmoking homes (n = 60), 18.15 µg/m^3 in smoking homes (n = 29), 5.29 µg/m^3 in nonsmoking workplaces (n = 51), and 22.80 µg/m^3 in smoking workplaces (n = 28). Differences in isoprene concentrations in personal air between nonsmoking and smoking sites were highly significant (Heavner et al., 1996). Another survey (Mukerjee et al., 1997) reported median summertime isoprene concentrations of 2.90 µg/m^3 in indoor air (n = 3; no information on whether occupants were smokers or nonsmokers) compared to 0.40 µg/m^3 in outdoor air (n = 1) in the Lower Rio Grande Valley (Texas).

REGULATIONS

EPA regulates isoprene under the Clean Air Act (CAA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Under the CAA, it is listed as a regulated flammable substance with a threshold quantity for accidental release prevention of 10,000 lb. Under the latter act, a final reportable quantity (RQ) of 100 lb (45.4 kg) for the compound has been established. FDA regulates isoprene as an indirect food additive in paper and paperboard components, in polymers, and in adjuvants, production aids, and sanitizers. OSHA regulates isoprene under the Hazard Communication Standard and as a hazardous chemical in laboratories.

The chief concern in the United States with natural or biogenic emissions of isoprene and other NMHCs has been secondary product formation leading to the production of ozone, aerosols, and other species of concern (Altschuller, 1983). The atmospheric reactions of ambient hydrocarbons during the summer months with airborne nitrogen oxides in some areas in the United States generate enough ozone to violate the National Ambient Air Quality Standard. To meet the air quality standard for ozone, States must consider biogenic emissions in their development of control strategies for anthropogenic emissions from stationary and mobile sources. Regulations are summarized in Volume II, Table B-75.